

Original Contribution

Benefits and Risks of Postmenopausal Hormone Therapy When It Is Initiated Soon After Menopause

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The authors further analyzed results from the Women's Health Initiative randomized trials (1993–2004) of conjugated equine estrogens, with or without medroxyprogesterone acetate, focusing on health benefits versus risks among women who initiated hormone therapy soon after menopause. Data from the Women's Health Initiative observational study (1993–2004) were included in some analyses for additional precision. Results are presented here for incident coronary heart disease, stroke, venous thromboembolism, breast cancer, colorectal cancer, endometrial cancer, or hip fracture; death from other causes; a summary global index; total cancer; and total mortality. Hazard ratios for breast cancer and total cancer were comparatively higher ($P < 0.05$) among women who initiated hormone therapy soon after menopause, for both regimens. Among these women, use of conjugated equine estrogens appeared to produce elevations in venous thromboembolism and stroke and a reduction in hip fracture. Estrogen plus progestin results among women who initiated use soon after menopause were similar for venous thromboembolism, stroke, and hip fracture but also included evidence of longer-term elevations in breast cancer, total cancer, and the global index. These analyses provide little support for the hypothesis of favorable effects among women who initiate postmenopausal estrogen use soon after menopause, either for coronary heart disease or for health benefits versus risk indices considered.

clinical trial; cohort studies; estrogens; estrogen replacement therapy; hormone replacement therapy; medroxyprogesterone 17-acetate; postmenopause; progestins

Abbreviations: CEE, conjugated equine estrogens; CHD, coronary heart disease; MPA, medroxyprogesterone acetate; WHI, Women's Health Initiative.

Editor's note: An invited commentary on this article appears on page 24.

The Women's Health Initiative (WHI) randomized controlled trials—trials of the use of 0.625 mg/day of conjugated equine estrogens (CEE) among 10,739 posthysterectomy women and CEE plus 2.5 mg/day of medroxyprogesterone acetate (MPA) among 16,608 women with an intact uterus—were designed to examine the effects of hormone therapy on coronary heart disease (CHD) risk and

overall health benefits versus risks. The trial design projected a major reduction in CHD risk, based on observational studies, for both regimens. Recruitment into both trials took place during 1993–1998. The CEE/MPA trial was stopped early in 2002 (1–8), after an average of 5.6 years of follow-up, on the basis of an elevation in breast cancer incidence in conjunction with an unfavorable global index—defined as time to incident CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, or hip fracture or to death from other causes. As a result, the potential use of this regimen for primary disease prevention was much reduced, and interest began to focus

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on the safety and efficacy of relatively short-term hormone therapy among recently postmenopausal women. This focus intensified after the CEE trial was also stopped early in 2004 (9–15), after an average of 7.1 years of follow-up, on the basis of an elevation in stroke in conjunction with a limited likelihood of demonstrating a CHD benefit. The global index in the CEE trial, defined as above but without endometrial cancer, differed little between randomization groups, reflecting a balance of health benefits and risks (9).

Among women who were assigned to active hormone therapy and reported no prior hormone therapy, only 10% in the CEE trial and 17% in the CEE/MPA trial were within 5 years of menopause at randomization. As such, effects of hormone therapy could not be estimated with precision for these important subsets. An additional sizeable group of women had used hormones prior to WHI enrollment and had either stopped hormone use or chosen to undergo a 3-month washout period prior to randomization. Approximately 84% of these women first initiated hormone therapy within 5 years following menopause in both the CEE and CEE/MPA trials. These women contribute information on health effects among women who initiate hormone therapy soon after menopause, particularly concerning benefits and risks some years after first use of hormone therapy.

The WHI observational study, carried out among 93,676 postmenopausal women in the same age range (50–79 years) at enrollment in 1993–1998, is available as an additional source of information on the health effects of these regimens. Women in the observational study were drawn from the same populations as the clinical trial women, and many elements of the protocol were common to the 2 WHI components. These included much baseline questionnaire and interview data, as well as the clinical outcomes ascertained and most aspects of the outcome ascertainment methods (16).

Results from joint analyses of clinical trial and observational study data have been reported for cardiovascular disease in relation to CEE/MPA (17) and CEE (18); hazard ratio estimates were in agreement between the clinical trials and the observational study for CHD and venous thromboembolism after allowing for confounding and time since hormone therapy initiation, though there was lesser agreement for stroke. Allowance for duration of hormone therapy use is essential in such analyses, since hormone therapy users in the observational study had often been on the regimen reported at enrollment for several preceding years, and hazard ratios declined with increasing duration of use for both CHD and venous thromboembolism. Similar analyses have been conducted for invasive breast cancer (19, 20). Hazard ratios were higher in the observational study than in the clinical trials for both CEE and CEE/MPA, even after consideration of confounding and duration of use. This residual discrepancy could be explained, however, by higher breast cancer hazard ratios among women who first used hormone therapy soon after menopause, as compared with those who initiated hormone therapy following a lengthy “gap” time. These analyses, suggesting comparatively unfavorable breast cancer effects among recently postmenopausal women, contrast with corresponding results for CHD (21) and coronary calcification (22) that may suggest more favorable effects among younger, recently postmenopausal women. A

“postmenopausal estrogen timing hypothesis,” suggesting that estrogens have favorable effects on CHD in recently postmenopausal women but null or harmful effects among older women, has been debated recently (23, 24), with WHI data being central to both sides of the argument. Of course, evaluation of a broader timing hypothesis involving a range of health effects is needed for decision-making concerning use of hormone therapy and is a major focus of this paper.

We analyzed the effects of CEE and CEE/MPA (particularly longer-term effects), when initiated soon after menopause, on a range of clinical outcomes, including the global index described above, as well as total invasive cancer incidence and total mortality. The analyses used both WHI clinical trial data and combined WHI clinical trial and observational study data.

MATERIALS AND METHODS

Study cohorts and prior hormone therapy

The cohorts examined here were the same as those described in previous reports (19, 20). The CEE clinical trial cohort comprised the 4,493 (84.6%) women assigned to active CEE and the 4,636 (85.4%) women assigned to placebo with a known age at menopause and a known age at first use of hormone therapy among prior hormone therapy users. A corresponding observational study subcohort of 20,117 women who had undergone hysterectomy prior to enrollment was also included. These women were either using the same 0.625 mg/day CEE regimen (10,582 women) as the women in the CEE trial or were not using any hormone therapy (9,535 women) at the time of WHI enrollment. To enhance comparability with the clinical trial eligibility criteria, we required these women to be without a personal history of breast cancer and to have had a mammogram within 2 years prior to enrollment. They were also required to have a known age at menopause and a known age at first use of hormone therapy. The same criteria led to the inclusion of 7,679 (90.3%) women assigned to active CEE/MPA and 7,509 (92.7%) women assigned to placebo in the CEE/MPA trial and to a subcohort of 30,942 women with an intact uterus at observational study enrollment, which included 6,756 women who were using the same CEE/MPA regimen (0.625 mg/day of CEE plus 2.5 mg/day of MPA) studied in the CEE/MPA trial and 24,186 women who were not using any hormone therapy at the time of enrollment.

Information on lifetime hormone use was obtained from clinical trial and observational study women at baseline by trained interviewers, assisted by structured questionnaires and charts displaying colored photographs of various hormone preparations. Detailed information was obtained on type of preparation, estrogen and progestin doses, schedule, and route of administration. Ages at starting and stopping the use of each preparation were recorded.

Follow-up and outcome ascertainment

Clinical outcomes were reported semiannually in the clinical trials and annually in the observational study (16).

Medical record documentation of these self-reports was obtained and diagnoses were confirmed at WHI clinical centers by physician adjudicators who were blinded to randomization assignment. In the clinical trials, all locally confirmed CHD, stroke, and venous thromboembolic events and deaths were further adjudicated by a central committee. A fraction of locally confirmed CHD and stroke events and deaths among observational study women were also centrally adjudicated, with good agreement being found (17) between local and central review. All locally confirmed breast, colonic, rectal, ovarian, and endometrial cancers and all hip fractures in both the clinical trials and the observational study were centrally reviewed and classified at the WHI Clinical Coordinating Center. Centrally adjudicated data were used here for centrally reviewed clinical outcomes; otherwise, locally determined outcome data were utilized.

Information on adherence to study hormone pills was obtained semiannually in the clinical trials, and information on the use of hormone therapy was updated annually by questionnaire in the observational study.

Statistical methods

Statistical methods and variable definitions were as defined in our previous reports (19, 20), where additional detail may be found. Briefly, follow-up in the hormone therapy trials continued through the end of the respective intervention periods, while corresponding observational study subcohorts were followed through December 15, 2004 (CEE) and February 28, 2003 (CEE/MPA), to produce corresponding average follow-up periods of 7.1 years and 5.5 years, respectively.

Age at menopause was defined as the lesser of 60 years, the age at which a woman had last had menstrual bleeding, the age at which a woman had undergone bilateral oophorectomy, or the age at which a woman had begun using postmenopausal hormone therapy. Age at menopause was considered missing if ages at last menstrual bleeding, bilateral oophorectomy, and hormone therapy initiation were each unavailable. Age at first use of hormone therapy was obtained from baseline interviews, and the "gap time" from menopause to first use of hormone therapy was calculated as the difference between these 2 ages.

Time from WHI enrollment was the "basic time variable" in Cox regression analyses (25) that stratified the data on cohort (clinical trials vs. observational study) and baseline age (in 5-year categories). Event times were censored when a woman first exceeded 2 years without a mammogram. Effects of hormone therapy are presented in terms of estimated hazard ratios. Hazard ratios among adherent women were obtained using these same methods, while censoring follow-up for a woman 6 months after a change from baseline hormone therapy user status, as in previous reports.

We addressed confounding in the observational study by including standard risk factors for each outcome in Cox regression models (listed in Web Table 1, which is posted on the *Journal's* Web site (<http://aje.oxfordjournals.org/>)). The set of risk factors to include was the same as in previous reports for cardiovascular disease and breast cancer (17–20)

and was otherwise based on the knowledge and experience of the investigator group, prior to data analysis. Observational study women who had missing values for any of the potentially confounding factors were excluded from corresponding analyses.

Cox model baseline incidence rates were also stratified on prior hormone therapy in combined clinical trial and observational study analyses. Confounding factor coefficients in the observational study were estimated separately in the prior-hormone-therapy and no-prior-hormone-therapy groups.

Prior hormone therapy use in the clinical trials and in the non-hormone-therapy groups in the observational study was defined relative to the time of WHI enrollment. Prior use for hormone therapy users in the observational study was defined relative to the beginning of the hormone therapy episode that was ongoing at enrollment. Going back in time, a change in hormone regimen or a usage gap of 1 year or longer defined a new hormone therapy episode.

Nominal 95% confidence intervals are presented for hazard ratio parameters, and 2-sided *P* values are reported.

RESULTS

Both the clinical trials and the observational study provided data on the health effects of these regimens among prior hormone therapy users and nonusers (Table 1). Regardless of baseline uterine status, age-adjusted incidence rates among nonuser groups without prior hormone therapy were comparable in the clinical trials and the observational study, with CHD (higher in the clinical trials) and death from other causes (higher in the observational study) being exceptions.

Clinical trial women without prior hormone therapy typically had much larger gap times from menopause to first use of hormone therapy than did clinical trial women with prior hormone therapy or observational study women with or without prior hormone therapy (Table 2).

Table 3 shows hazard ratio estimates for CEE and CEE/MPA from the clinical trials classified according to prior hormone therapy and gap time from menopause to first use of hormone therapy (<5 years vs. ≥5 years). Hazard ratio estimates are not presented if there were fewer than 4 events among hormone therapy users. Most information on CEE effects among women who started hormone therapy within 5 years following menopause was derived from women who had used hormone therapy prior to WHI enrollment. Data from these women suggested possible elevations in risk of stroke, venous thromboembolism, the global index, and total mortality and a possible reduction in hip fracture risk with CEE. Only for the global index, however, was there evidence (*P* = 0.05) of less favorable results for women with relatively short gap times as compared with longer gap times (<5 vs. ≥5 years). These results may have been influenced by the nature and duration of the hormone therapy used prior to randomization. Table 3 also provides some evidence for an increase in CHD and venous thromboembolism with CEE/MPA among women who started hormone therapy within 5 years of menopause. Also note

Table 1. Age-adjusted Incidence Rates for Selected Clinical Outcomes, According to Prior^a Use of Hormone Therapy and Use of Conjugated Equine Estrogens (Posthysterectomy Women) or Conjugated Equine Estrogens/Medroxyprogesterone Acetate (Women With Intact Uterus), in the Women's Health Initiative Hormone Therapy Clinical Trials and Corresponding Observational Study Subcohorts, 1993–2004

	Clinical Trials				Observational Study			
	No Prior HT		Prior HT		No Prior HT		Prior HT	
	<i>Women Without Uterus</i>							
	Placebo	CEE	Placebo	CEE	Nonuser	CEE	Nonuser	CEE
No. of women	1,977	1,952	2,659	2,541	5,106	8,677	4,429	1,905
Average age, years	64.1	63.8	63.4	63.6	65.0	63.4	65.7	64.2
Incidence rate ^b (no. of cases):								
Coronary heart disease	7.07 (98)	5.79 (83)	4.28 (79)	5.05 (89)	4.33 (171)	2.45 (147)	3.42 (123)	2.73 (38)
Stroke	3.05 (43)	4.67 (68)	3.61 (67)	4.43 (78)	3.31 (122)	2.89 (171)	3.16 (117)	3.73 (52)
Venous thromboembolism	2.49 (32)	2.70 (32)	2.04 (38)	3.31 (59)	2.23 (93)	1.68 (101)	1.97 (65)	1.23 (18)
Invasive breast cancer	3.73 (49)	2.28 (30)	2.67 (50)	2.56 (46)	3.22 (122)	3.81 (235)	3.12 (99)	3.48 (51)
Invasive colorectal cancer	1.52 (22)	1.65 (23)	1.21 (23)	1.47 (26)	1.31 (54)	0.73 (46)	0.86 (33)	1.66 (24)
Hip fracture	1.89 (24)	1.53 (21)	1.95 (35)	0.95 (17)	1.38 (48)	0.96 (58)	1.28 (51)	1.66 (21)
Death from other causes	4.78 (67)	5.51 (69)	4.52 (84)	4.79 (85)	6.58 (246)	4.57 (274)	6.23 (223)	4.63 (62)
Global index	21.57 (300)	20.82 (285)	17.20 (320)	19.44 (345)	19.70 (753)	15.32 (928)	18.41 (650)	17.11 (237)
Total invasive cancer	10.54 (148)	9.25 (131)	9.15 (171)	8.87 (158)	10.15 (386)	9.23 (571)	10.33 (348)	9.73 (138)
Total mortality	8.50 (119)	8.17 (106)	6.70 (124)	7.93 (140)	9.29 (357)	6.38 (382)	9.11 (330)	6.55 (87)
	<i>Women With Uterus</i>							
	Placebo	CEE/MPA	Placebo	CEE/MPA	Nonuser	CEE/MPA	Nonuser	CEE/MPA
No. of women	5,427	5,450	2,082	2,229	18,526	5,710	5,660	1,046
Average age, years	63.6	63.7	63.0	62.6	64.7	60.7	64.8	64.3
Incidence rate ^b (no. of cases):								
Coronary heart disease	3.52 (198)	3.92 (116)	2.66 (31)	4.33 (52)	2.76 (306)	2.07 (50)	2.53 (92)	1.70 (10)
Stroke	2.42 (74)	3.36 (96)	2.48 (27)	2.81 (34)	2.17 (245)	1.65 (37)	2.31 (84)	1.42 (8)
Venous thromboembolism	1.58 (43)	3.62 (110)	2.04 (23)	3.32 (40)	1.64 (186)	2.35 (60)	1.72 (59)	1.00 (6)
Invasive breast cancer	3.48 (105)	3.91 (114)	2.50 (28)	4.65 (58)	2.85 (291)	6.75 (199)	3.45 (110)	7.44 (43)
Invasive colorectal cancer	1.64 (43)	1.00 (31)	1.53 (17)	0.70 (8)	0.97 (106)	1.08 (27)	1.06 (35)	0.72 (4)
Invasive endometrial cancer	0.62 (19)	0.49 (12)	0.88 (10)	0.91 (10)	0.77 (79)	1.07 (30)	1.17 (40)	1.05 (6)
Hip fracture	1.65 (48)	1.32 (39)	1.74 (19)	0.57 (7)	1.22 (140)	1.45 (23)	0.97 (37)	1.77 (10)
Death from other causes	3.83 (108)	3.71 (110)	3.99 (46)	3.10 (36)	4.44 (476)	3.68 (86)	3.92 (141)	2.62 (15)
Global index	16.47 (478)	18.47 (540)	15.69 (177)	17.32 (209)	15.36 (1,668)	18.04 (469)	15.63 (542)	17.38 (100)
Total invasive cancer	10.26 (303)	9.79 (282)	10.02 (114)	11.70 (141)	9.01 (956)	13.32 (370)	9.38 (311)	12.38 (71)
Total mortality	5.25 (150)	5.42 (156)	5.59 (64)	5.10 (60)	5.93 (640)	4.71 (112)	5.45 (198)	3.47 (20)

Abbreviations: CEE, conjugated equine estrogens; HT, hormone therapy; MPA, medroxyprogesterone acetate.

^a Prior HT was defined relative to Women's Health Initiative enrollment in the clinical trials and in the nonuser groups in the observational study. Prior HT in the user groups in the observational study was defined relative to the beginning of the ongoing HT episode at enrollment.^b Incidence rate per 1,000 person-years, adjusted to the 5-year age distribution in the clinical trials.

the greater hazard ratio elevation ($P = 0.03$) for invasive breast cancer among such women (20). For CEE/MPA, the global index pointed nonsignificantly in the unfavorable direction, while total mortality and deaths from "other" causes pointed nonsignificantly in the favorable direction, among women with gap times less than 5 years.

Table 4 shows estimated hazard ratios for women who began hormone therapy immediately following menopause, based on analysis of combined data from the clinical trials and the observational study. These analyses allowed the hazard ratio to depend multiplicatively on gap time from

menopause to first use of hormone therapy, with gap times greater than 15 years being recoded as 15 years, as in previous analyses (19, 20). We also made a provision in these analyses for residual confounding in the observational study by including a multiplicative factor for the hormone therapy hazard ratio in the observational study divided by the hormone therapy hazard ratio in the clinical trials. A departure from unity for this factor could suggest important residual confounding in the observational study.

Prior hormone therapy users who initiated CEE/MPA evidently experienced an elevated CHD risk within the first

Table 2. Distribution of Subjects and Clinical Outcomes in the Women's Health Initiative Clinical Trials and Corresponding Observational Study Subcohorts, According to Prior^a Use of Postmenopausal Hormone Therapy and Gap Time From Menopause to First Use of Hormone Therapy Among Hormone Users, 1993–2004

	Gap Time, years											
	Clinical Trials						Observational Study					
	No Prior HT			Prior HT			No Prior HT			Prior HT		
	<5	5–14	≥15	<5	5–14	≥15	<5	5–14	≥15	<5	5–14	≥15
<i>Use of Conjugated Equine Estrogens</i>												
No. of women	198	618	1,136	2,129	294	113	6,626	1,454	597	1,662	213	30
% of women	10	32	58	84	12	4	76	17	7	87	11	2
No. of cases												
Coronary heart disease	2	22	59	76	8	5	104	28	15	31	6	1
Stroke	3	19	46	72	3	3	119	39	13	42	7	3
Venous thromboembolism	1	6	25	51	4	4	59	30	12	15	3	0
Invasive breast cancer	4	5	21	40	4	2	188	36	11	46	5	0
Invasive colorectal cancer	1	6	16	26	0	0	37	6	3	23	1	0
Hip fracture	2	5	14	15	2	0	44	9	5	19	2	0
Death from other causes	3	15	51	76	7	2	201	43	30	50	11	1
Global index	15	68	202	308	22	15	689	164	75	203	29	5
Total invasive cancer	16	28	87	145	8	5	436	101	34	123	14	1
Total mortality	6	21	79	125	10	5	275	69	38	69	15	3
<i>Use of Conjugated Equine Estrogens/Medroxyprogesterone Acetate</i>												
No. of women	952	2,338	2,160	1,864	302	63	4,257	1,115	338	916	113	17
% of women	17	43	40	84	14	3	75	20	6	88	11	2
No. of cases												
Coronary heart disease	10	35	71	43	5	4	30	13	7	8	2	0
Stroke	6	37	53	28	3	3	27	7	3	8	0	0
Venous thromboembolism	8	50	52	35	5	0	39	13	8	3	3	0
Invasive breast cancer	22	46	46	51	6	1	160	34	5	40	3	0
Invasive colorectal cancer	2	14	15	5	3	0	20	4	3	2	1	1
Invasive endometrial cancer	2	5	5	7	1	2	25	3	2	6	0	0
Hip fracture	0	9	30	4	2	1	10	7	6	7	2	1
Death from other causes	8	41	61	29	7	0	51	21	14	12	3	0
Global index	54	205	281	171	29	9	340	88	41	85	13	2
Total invasive cancer	35	114	133	117	20	4	284	66	20	64	6	1
Total mortality	11	53	92	48	9	3	72	23	17	16	4	0

Abbreviation: HT, hormone therapy.

^a Prior HT was defined relative to Women's Health Initiative enrollment in the clinical trials and in the nonuser groups in the observational study. Prior HT in the user groups in the observational study was defined relative to the beginning of the ongoing HT episode at enrollment.

2 years of restarting hormone therapy. The hazard ratio for CEE was estimated to increase by a factor of 1.03 with an increase of 5 years in gap time, but this factor was not significantly different from 1. In addition, the ratio of the overall hazard ratio in the observational study to that in the clinical trials was not significantly different from 1 (estimated as 0.91 for CEE and 0.99 for CEE/MPA) for either regimen, providing little suggestion of residual confounding for CHD in the observational study.

The stroke hazard ratios did not appear to depend on time from menopause to first use of hormone therapy for either

regimen, so the previously noted stroke hazard ratio elevations may apply to recently postmenopausal women. There was evidence of disagreement between hazard ratios from the 2 cohorts, however, with hazard ratios from the observational study being approximately 40% lower than those from the clinical trials.

The venous thromboembolism hazard ratio for CEE may have increased with increasing years from menopause to first use of hormone therapy; there was evidence for an increased risk among women who started hormone therapy soon after menopause, which was derived mainly from prior

Table 3. Estimated Hazard Ratios for Selected Clinical Outcomes According to Use of Conjugated Equine Estrogens and Conjugated Equine Estrogens/Medroxyprogesterone Acetate, by Years From Menopause to First Use of Hormone Therapy and Prior Hormone Therapy in the Women's Health Initiative Clinical Trials, 1993–2004

	Use of Conjugated Equine Estrogens					Use of Conjugated Equine Estrogens/ Medroxyprogesterone Acetate				
	Time From Menopause to First Use of HT, years				P for Gap Time Interaction ^a	Time From Menopause to First Use of HT, years				P for Gap Time Interaction ^a
	<5		≥5			<5		≥5		
	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	
Coronary heart disease										
No prior HT ^b	— ^c		0.89	0.67, 1.20	0.40	0.99	0.49, 1.98	1.19	0.91, 1.57	0.42
Prior HT	1.22	0.89, 1.67	1.04	0.58, 1.86		1.57	0.99, 2.50	1.45	0.69, 3.06	
Stroke										
No prior HT	—		1.64	1.12, 2.41	0.96	0.92	0.38, 2.24	1.31	0.96, 1.79	1.00
Prior HT	1.36	0.98, 1.90	0.56	0.20, 1.28		1.20	0.71, 2.03	1.10	0.46, 2.68	
Venous thromboembolism										
No prior HT	—		1.07	0.65, 1.76	0.65	2.26	1.00, 5.10	2.59	1.81, 3.71	0.45
Prior HT	1.71	1.12, 2.60	1.37	0.64, 2.95		1.78	1.05, 3.02	1.07	0.40, 2.81	
Invasive breast cancer										
No prior HT	1.12	0.39, 3.21	0.58	0.36, 0.93	0.20	1.77	1.07, 2.93	0.99	0.74, 1.31	0.03
Prior HT	1.00	0.66, 1.51	0.77	0.33, 1.80		2.06	1.30, 3.27	1.30	0.57, 2.99	
Invasive colorectal cancer										
No Prior HT	—		1.10	0.61, 1.99	0.34	—		0.72	0.42, 1.16	0.42
Prior HT	1.43	0.82, 2.51	—			0.35	0.13, 0.94	—		
Invasive endometrial cancer										
No prior HT	—		—		—	—		0.57	0.26, 1.22	0.97
Prior HT	—		—			0.80	0.31, 2.11	—		
Hip fracture										
No prior HT	—		0.87	0.48, 1.60	0.58	—		0.81	0.53, 1.24	0.04
Prior HT	0.54	0.30, 0.99	—			0.25	0.09, 0.74	—		
Death from other causes ^d										
No prior HT	1.15	0.50, 2.69	0.91	0.70, 1.19	0.14	0.66	0.31, 1.40	1.05	0.80, 1.37	0.21
Prior HT	1.27	0.99, 1.63	0.76	0.45, 1.30		0.69	0.44, 1.11	0.79	0.36, 1.76	
Global index ^e										
No prior HT	0.90	0.53, 1.53	0.98	0.83, 1.16	0.05	1.13	0.84, 1.53	1.12	0.99, 1.28	0.93
Prior HT	1.22	1.04, 1.43	0.71	0.50, 1.00		1.11	0.90, 1.37	1.09	0.77, 1.55	
Total invasive cancer										
No prior HT	1.72	1.00, 2.94	0.84	0.66, 1.07	0.07	1.07	0.73, 1.55	0.90	0.76, 1.07	0.25
Prior HT	1.07	0.85, 1.33	0.48	0.27, 0.84		1.17	0.90, 1.52	1.08	0.69, 1.67	
Total mortality										
No prior HT	1.15	0.50, 2.69	0.91	0.70, 1.19	0.14	0.73	0.38, 1.39	1.05	0.84, 1.33	0.36
Prior HT	1.27	0.99, 1.63	0.76	0.45, 1.30		0.83	0.57, 1.21	0.95	0.51, 1.76	

Abbreviations: CI, confidence interval; HR, hazard ratio; HT, hormone therapy.

^a Interaction “score” test for product term between indicator variables for HT and gap time greater than or equal to 5 years in a Cox model that allowed both the incidence rate and the HT hazard ratio to depend on prior HT.^b Prior postmenopausal HT was defined relative to enrollment in the Women's Health Initiative clinical trials.^c HRs (and 1 *P* value) are not presented if there were fewer than 4 events among HT users.^d Death from causes other than cardiovascular disease, breast cancer, colorectal cancer, endometrial cancer, or hip fracture.^e The global index is the time to first occurrence of the outcome listed above it, as well as noninvasive breast, colorectal, or endometrial cancer.

Table 4. Estimated Hazard Ratios for Selected Clinical Outcomes According to Use of Conjugated Equine Estrogens and Conjugated Equine Estrogens/Medroxyprogesterone Acetate Among Women who Began Hormone Therapy Immediately Following Menopause, From Combined Analysis of Women's Health Initiative Clinical Trial and Observational Study Data, 1993–2004

	Years From HT Initiation Among Women With No Prior Use of HT						Years From "Current" HT Episode ^a Among Women With Prior Use of HT						5-Year ^b Increase in Gap Time		Ratio ^c of HR in Observational Study to HR in Clinical Trials	
	<2		2–4		≥5		<2		2–4		≥5		HR	95% CI	HR	95% CI
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI				
Coronary heart disease																
CEE	1.06	0.56, 2.02	0.87	0.51, 1.48	0.69	0.46, 1.04	1.33	0.69, 2.56	1.40	0.90, 2.19	0.87	0.59, 1.28	1.03	0.92, 1.15	0.91	0.62, 1.32
CEE/MPA	1.26	0.72, 2.18	1.11	0.64, 1.91	0.88	0.50, 1.55	3.03	1.36, 6.75	1.12	0.61, 2.04	1.23	0.61, 2.51	1.01	0.87, 1.19	0.99	0.61, 1.62
Stroke																
CEE	1.75	0.83, 3.71	1.76	0.92, 3.34	1.68	1.06, 2.66	1.56	0.72, 3.41	0.95	0.58, 1.54	1.57	1.04, 2.36	0.96	0.86, 1.08	0.68	0.44, 1.04
CEE/MPA	1.68	0.82, 3.42	1.63	0.88, 3.02	1.78	0.93, 3.40	1.39	0.52, 3.75	1.46	0.76, 2.80	0.75	0.33, 1.71	0.90	0.75, 1.09	0.55	0.31, 0.99
Venous thromboembolism																
CEE	0.94	0.35, 2.51	0.89	0.41, 1.93	0.84	0.47, 1.51	2.93	1.02, 8.40	1.46	0.79, 2.69	1.02	0.62, 1.66	1.13	0.98, 1.31	0.74	0.43, 1.26
CEE/MPA	5.30	2.58, 10.89	2.17	1.16, 4.04	2.12	1.16, 3.89	1.83	0.81, 4.13	2.03	1.01, 4.07	0.61	0.24, 1.54	0.95	0.80, 1.14	0.79	0.46, 1.36
Invasive breast cancer																
CEE	1.17	0.46, 2.98	1.17	0.65, 2.11	0.91	0.55, 1.50	1.35	0.62, 2.94	0.80	0.46, 1.39	0.95	0.58, 1.56	0.83	0.72, 0.95	1.25	0.78, 2.01
CEE/MPA	0.98	0.55, 1.74	1.99	1.30, 3.04	2.79	1.82, 4.30	1.26	0.65, 2.45	2.59	1.53, 4.39	3.04	1.62, 5.70	0.81	0.71, 0.92	1.03	0.69, 1.53
Invasive colorectal cancer																
CEE	1.44	0.49, 4.21	1.71	0.54, 5.44	1.23	0.53, 2.88	0.82	0.29, 2.35	0.87	0.37, 2.06	2.78	1.22, 6.35	0.88	0.69, 1.12	0.56	0.25, 1.23
CEE/MPA	0.73	0.26, 2.05	0.51	0.21, 1.26	0.55	0.21, 1.44	0.52	0.13, 2.11	0.30	0.08, 1.11	0.56	0.18, 1.78	1.08	0.81, 1.44	1.94	0.85, 4.42
Invasive endometrial cancer																
CEE/MPA	0.95	0.20, 4.62	0.97	0.35, 2.70	1.78	0.68, 4.65	0.36	0.07, 1.74	0.89	0.32, 2.48	0.72	0.23, 2.27	0.88	0.65, 1.18	0.97	0.40, 2.38
Hip fracture																
CEE	0.70	0.12, 4.03	0.73	0.24, 2.20	1.18	0.55, 2.55	0.86	0.20, 3.75	0.49	0.19, 1.27	0.73	0.39, 1.38	0.93	0.75, 1.16	0.77	0.38, 1.57
CEE/MPA	0.28	0.10, 0.80	0.37	0.15, 0.93	0.23	0.09, 0.56	0.81	0.21, 3.17	0.32	0.11, 0.93	0.44	0.13, 1.46	1.34	1.02, 1.75	2.74	1.35, 5.54
Death from other causes ^d																
CEE	1.13	0.50, 2.56	0.92	0.54, 1.60	1.14	0.77, 1.68	0.85	0.39, 1.89	0.78	0.50, 1.23	1.59	1.11, 2.30	1.01	0.91, 1.11	0.69	0.48, 0.99
CEE/MPA	0.91	0.46, 1.82	0.66	0.40, 1.06	0.96	0.58, 1.60	0.35	0.09, 1.32	0.71	0.43, 1.19	0.75	0.39, 1.43	1.13	0.98, 1.30	0.87	0.56, 1.37
Global index ^e																
CEE	1.22	0.86, 1.72	1.12	0.86, 1.46	1.04	0.85, 1.27	1.18	0.84, 1.65	0.97	0.78, 1.21	1.25	1.04, 1.51	0.96	0.91, 1.02	0.84	0.70, 1.02
CEE/MPA	1.34	1.04, 1.74	1.23	0.99, 1.54	1.45	1.16, 1.81	1.16	0.82, 1.66	1.17	0.91, 1.50	1.13	0.84, 1.52	0.94	0.88, 1.00	1.01	0.83, 1.23
Total invasive cancer																
CEE	1.54	0.96, 2.47	1.19	0.83, 1.70	1.12	0.84, 1.49	0.96	0.62, 1.50	0.70	0.51, 0.97	1.36	1.03, 1.79	0.90	0.83, 0.97	0.81	0.62, 1.06
CEE/MPA	1.03	0.73, 1.45	1.22	0.93, 1.60	1.55	1.18, 2.05	0.84	0.55, 1.29	1.37	1.01, 1.86	1.19	0.83, 1.72	0.90	0.83, 0.98	1.13	0.88, 1.44
Total mortality																
CEE	1.34	0.70, 2.54	0.99	0.64, 1.53	1.00	0.74, 1.37	1.42	0.77, 2.64	1.00	0.70, 1.42	1.25	0.94, 1.67	0.97	0.89, 1.05	0.79	0.59, 1.05
CEE/MPA	0.84	0.48, 1.47	0.79	0.52, 1.19	1.07	0.69, 1.66	0.75	0.31, 1.78	0.94	0.62, 1.43	0.71	0.41, 1.24	1.07	0.95, 1.21	0.84	0.57, 1.24

Abbreviations: CEE, conjugated equine estrogens; CI, confidence interval; HR, hazard ratio; HT, hormone therapy; MPA, medroxyprogesterone acetate.

^a "Years from 'current' HT episode" refers to years from randomization in the clinical trials and years from the beginning of the HT episode ongoing at the time of enrollment in the observational study (see Materials and Methods).^b HRs for CEE or CEE/MPA were estimated to change by this factor with a 5-year increase in gap time from menopause to first use of HT.^c Estimate of the overall ratio of CEE or CEE/MPA HRs between the observational study and the clinical trials, after controlling for the factors described in the text (see Materials and Methods).^d Death from causes other than cardiovascular disease, breast cancer, colorectal cancer, endometrial cancer, or hip fracture.^e The global index is the time to first occurrence of the outcome listed above it (with breast, colorectal, and endometrial cancer, including noninvasive cancer).

hormone therapy users. The hazard ratio for CEE/MPA showed strong early elevations among recently postmenopausal women without prior hormone therapy.

As was previously reported (19, 20), invasive breast cancer hazard ratios decreased with increasing gap time for both regimens. Combined clinical trial and observational study analyses suggested that recently postmenopausal women experienced hazard ratio elevations after a few years of CEE/MPA, whereas no clear hazard ratio effects were suggested for CEE.

Chlebowski et al. (6) reported a 40% lower invasive colorectal cancer hazard ratio among CEE/MPA users in the clinical trials, but this reduction was accompanied by a more advanced stage of disease at diagnosis. The ratio of the hazard ratio for CEE/MPA from the observational study to that from the clinical trials (Table 4) was 1.94 (95% confidence interval: 0.85, 4.42), suggesting that this hazard ratio reduction was not observed in the observational study data. In contrast, this same ratio was 0.56 (95% confidence interval: 0.25, 1.23) for CEE, and there was a suggestion of a longer-term hazard ratio elevation among women initiating hormone therapy soon after menopause. Results from more detailed colorectal cancer analyses that attempt to elucidate the effects of hormone therapy on diagnosis have recently been presented elsewhere (26).

The use of CEE/MPA soon after menopause did not show any clear effect on invasive endometrial cancer incidence. Overall hazard ratios agreed closely between the clinical trials and the observational study.

Hazard ratios for hip fracture among recently postmenopausal women tended to be reduced with either CEE or CEE/MPA, though the numbers of cases were small. Note that the hazard ratio for CEE/MPA was substantially higher in the observational study than in the clinical trials, possibly reflecting a tendency to prescribe this regimen to women at elevated risk of fracture.

"Deaths from other causes" included all deaths not preceded by a diagnosis of 1 or more of the outcomes listed above it (or by noninvasive breast, colorectal, or endometrial cancer) during WHI follow-up. Hazard ratios for CEE in the observational study were lower overall than those in the clinical trials, suggesting possible residual confounding in the observational study.

The global index hazard ratio was elevated for CEE/MPA and possibly also some years after starting CEE among prior hormone therapy users. The global index hazard ratio for CEE/MPA may have been higher among recently postmenopausal women than among women with long gap times, partly reflecting elevations in breast cancer risk.

Hazard ratios for total invasive cancer similarly appeared to be elevated among recently postmenopausal women following a few years of CEE/MPA use and may also have been elevated after a few years of CEE use among prior hormone therapy users. Note also that total cancer hazard ratios were lower among women with longer gap times for both CEE and CEE/MPA. In comparison, the hazard ratio for total mortality did not seem to be much affected by either regimen among women initiating hormone therapy at menopause.

Table 5 shows analyses corresponding to those of Table 4, with the follow-up time for a woman being censored 6

months after a change in hormone therapy user group status. The trends noted from Table 4 generally persisted in these comparisons among adherent women. Differences in overall hormone therapy hazard ratios between the clinical trials and the observational study tended to be accentuated in comparison with Table 4, raising concerns about observational analyses of hormone therapy and stroke (CEE and CEE/MPA), hip fracture (CEE/MPA), death from other causes (CEE), the global index (CEE), and total mortality (CEE), especially in the absence of the type of residual confounding provision made here. Some hazard ratios presented in Tables 4 and 5 were not precisely estimated. Web Table 2 (<http://aje.oxfordjournals.org/>) shows the numbers of clinical outcomes among hormone therapy users in the observational study that contributed to hazard ratio estimation, following the exclusion of observational study women with missing data on potentially confounding factors in Table 4, and numbers of contributing clinical outcomes among hormone therapy users in the clinical trials and the observational study following the adherence-related censoring of Table 5.

Tables 4 and 5 suggest CEE and CEE/MPA hazard ratios that were comparatively higher among women who had relatively short gap times, not only for invasive breast cancer as previously reported (19, 20) but also for total invasive cancer and, for CEE/MPA, possibly the global index. To examine whether these gap time differences could be attributed to relatively longer durations of hormone therapy among women with short gap times, we repeated the total invasive cancer and global index analyses of Tables 4 and 5 with the addition of a linear interaction term for the interaction between years from hormone therapy initiation and hormone therapy group assignment in the log hazard ratio model. For total invasive cancer, the gap time association remained significant (all P 's < 0.05), and the 5-year gap time hazard ratio effects were essentially unchanged from those shown in Tables 4 and 5 for both CEE and CEE/MPA. For CEE/MPA and the global index, however, the gap time association was not significant ($P = 0.28$ in Table 4 and $P = 0.12$ in Table 5), while there was some evidence for larger hazard ratios with longer durations of use ($P = 0.003$ in Table 4 and $P = 0.04$ in Table 5) beyond the hazard ratio dependence on duration acknowledged through separate hazard ratios for <2, 2–4, and ≥ 5 years from hormone therapy initiation.

DISCUSSION

The effects of CEE and CEE/MPA did not depend significantly on gap time from menopause to first use of hormone therapy for most clinical outcomes considered, either in further analyses of clinical trial data or in combined clinical trial and observational study data analyses. An important exception was breast cancer (19, 20), where hazard ratios tended to be higher among women who initiated hormone therapy soon after menopause as compared with women who had longer gap times. In part because of the breast cancer results, the total invasive cancer hazard ratios were also comparatively higher among women who started using

Table 5. Estimated Hazard Ratios for Selected Clinical Outcomes According to Use of Conjugated Equine Estrogens and Conjugated Equine Estrogens/Medroxyprogesterone Acetate Among Women who Began Hormone Therapy Immediately Following Menopause and Adhered to Their Hormone Therapy Regimen, From Combined Analysis of Women's Health Initiative Clinical Trial and Observational Study Data, 1993–2004

	Years From HT Initiation Among Women With No Prior Use of HT						Years From "Current" HT Episode ^a Among Women With Prior Use of HT						5-Year ^b Increase in Gap Time		Ratio ^c of HR in Observational Study to HR in Clinical Trials	
	<2		2–4		≥5		<2		2–4		≥5		HR	95% CI	Ratio	95% CI
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI				
Coronary heart disease																
CEE	1.12	0.55, 2.24	0.99	0.49, 2.00	0.60	0.35, 1.04	1.26	0.64, 2.46	1.52	0.81, 2.86	0.86	0.48, 1.52	0.98	0.85, 1.12	1.05	0.63, 1.76
CEE/MPA	1.42	0.76, 2.65	1.37	0.71, 2.67	1.24	0.61, 2.50	2.70	1.11, 6.52	1.10	0.46, 2.63	2.18	0.77, 6.19	1.01	0.84, 1.22	0.76	0.41, 1.42
Stroke																
CEE	1.49	0.68, 3.28	2.45	1.06, 5.65	2.46	1.29, 4.70	1.43	0.61, 3.39	1.56	0.81, 3.03	2.39	1.25, 4.56	1.01	0.89, 1.15	0.46	0.25, 0.84
CEE/MPA	1.58	0.69, 3.66	2.17	0.99, 4.80	3.48	1.36, 8.96	1.73	0.53, 5.59	1.05	0.45, 2.45	1.48	0.51, 4.29	0.91	0.72, 1.14	0.33	0.14, 0.78
Venous thromboembolism																
CEE	1.12	0.40, 3.17	0.80	0.30, 2.15	0.99	0.46, 2.14	4.09	1.28, 13.11	2.19	0.97, 4.95	1.56	0.73, 3.31	1.12	0.95, 1.33	0.61	0.30, 1.26
CEE/MPA	6.44	2.79, 14.85	3.15	1.47, 6.74	2.69	1.28, 5.63	1.65	0.70, 3.89	2.37	0.88, 6.43	1.64	0.41, 6.59	1.01	0.83, 1.23	0.62	0.32, 1.20
Invasive breast cancer																
CEE	1.44	0.54, 3.84	1.15	0.57, 2.32	1.00	0.54, 1.84	1.63	0.68, 3.91	0.82	0.42, 1.57	0.91	0.49, 1.69	0.85	0.73, 0.98	1.07	0.60, 1.93
CEE/MPA	1.05	0.56, 1.97	2.18	1.31, 3.63	3.15	1.90, 5.20	1.79	0.84, 3.83	4.02	2.03, 7.98	3.14	1.46, 6.75	0.80	0.69, 0.93	1.06	0.66, 1.71
Invasive colorectal cancer																
CEE	1.42	0.45, 4.52	1.91	0.44, 8.37	2.12	0.55, 8.16	0.95	0.32, 2.82	0.44	0.12, 1.66	4.43	1.13, 17.38	0.90	0.67, 1.21	0.32	0.09, 1.17
CEE/MPA	0.54	0.16, 1.77	0.46	0.16, 1.36	0.50	0.16, 1.58	0.53	0.13, 2.22	0.27	0.06, 1.28	0.71	0.17, 3.07	1.21	0.88, 1.68	1.85	0.68, 5.01
Invasive endometrial cancer																
CEE/MPA	1.50	0.21, 10.67	1.60	0.40, 6.45	1.97	0.54, 7.13	0.33	0.04, 2.87	0.56	0.14, 2.31	0.82	0.17, 3.90	0.72	0.48, 1.09	1.13	0.35, 3.67
Hip fracture																
CEE	0.46	0.04, 4.88	0.53	0.11, 2.51	0.69	0.19, 2.56	0.60	0.11, 3.24	0.13	0.02, 1.08	0.54	0.16, 1.76	1.01	0.77, 1.31	0.96	0.28, 3.32
CEE/MPA	0.35	0.10, 1.17	0.33	0.10, 1.10	0.22	0.07, 0.71	0.94	0.19, 4.58	0.26	0.05, 1.25	0.43	0.09, 2.07	1.29	0.94, 1.78	3.10	1.20, 7.98
Death from other causes ^d																
CEE	1.26	0.42, 3.81	1.04	0.43, 2.53	1.88	0.90, 3.93	1.29	0.51, 3.21	0.82	0.41, 1.63	3.16	1.53, 6.55	1.01	0.90, 1.14	0.38	0.18, 0.76
CEE/MPA	0.96	0.43, 2.14	0.70	0.34, 1.42	0.87	0.40, 1.88	0.18	0.02, 1.47	0.69	0.30, 1.61	0.75	0.26, 2.13	1.09	0.91, 1.31	0.97	0.48, 1.95
Global index ^e																
CEE	1.26	0.86, 1.83	1.23	0.87, 1.75	1.18	0.89, 1.57	1.29	0.90, 1.85	1.03	0.76, 1.39	1.53	1.15, 2.03	0.97	0.91, 1.03	0.70	0.53, 0.91
CEE/MPA	1.53	1.14, 2.05	1.56	1.18, 2.06	1.89	1.42, 2.49	1.28	0.86, 1.91	1.32	0.94, 1.85	1.43	0.96, 2.11	0.92	0.85, 0.99	0.86	0.67, 1.11
Total invasive cancer																
CEE	1.72	1.04, 2.83	1.07	0.68, 1.69	1.17	0.80, 1.70	1.12	0.70, 1.81	0.74	0.49, 1.11	1.40	0.96, 2.02	0.91	0.83, 0.99	0.77	0.54, 1.11
CEE/MPA	1.14	0.78, 1.67	1.49	1.08, 2.07	1.82	1.31, 2.53	1.01	0.64, 1.61	1.48	0.99, 2.22	1.42	0.90, 2.25	0.88	0.80, 0.97	1.06	0.79, 1.43
Total mortality																
CEE	1.62	0.75, 3.53	1.26	0.66, 2.41	1.35	0.82, 2.24	2.19	1.08, 4.47	1.06	0.62, 1.83	1.92	1.16, 3.19	0.97	0.88, 1.07	0.53	0.33, 0.86
CEE/MPA	0.83	0.43, 1.60	0.89	0.50, 1.60	1.13	0.59, 2.16	0.55	0.18, 1.63	0.84	0.43, 1.66	0.90	0.38, 2.14	1.09	0.93, 1.27	0.76	0.43, 1.37

Abbreviations: CEE, conjugated equine estrogens; CI, confidence interval; HR, hazard ratio; HT, hormone therapy; MPA, medroxyprogesterone acetate.

^a "Years from 'current' HT episode" refers to years from randomization in the clinical trials and years from the beginning of the HT episode ongoing at the time of enrollment in the observational study (see Materials and Methods).^b HRs for CEE or CEE/MPA were estimated to change by this factor with a 5-year increase in gap time from menopause to first use of HT.^c Estimate of the overall ratio of CEE or CEE/MPA HRs between the observational study and the clinical trials, after controlling for the factors described in the text (see Materials and Methods).^d Death from causes other than cardiovascular disease, breast cancer, colorectal cancer, endometrial cancer, or hip fracture.^e The global index is the time to first occurrence of the outcome listed above it (with breast, colorectal, and endometrial cancer, including noninvasive cancer).

CEE or CEE/MPA soon after menopause, as were the global index hazard ratios for CEE/MPA.

The interpretation of these hazard ratio effects is complicated, for several reasons. First, there is the multiple testing issue. One would expect approximately 3 of the 95% confidence intervals in Tables 4 and 5 to exclude 1 by chance alone. Another reason for a cautious interpretation, and a limitation of the current analyses more generally, is that hazard ratios pertaining to 5 or more years from hormone therapy initiation were derived mainly from the observational study. In addition, there were few recently postmenopausal women without prior hormone therapy who were followed in WHI during their early years of hormone therapy use, so corresponding hazard ratios were imprecisely estimated and may have depended on modeling assumptions.

Cohort studies that enroll large numbers of women prior to menopause and follow them for some years beyond menopause can be expected to have greater precision for estimating these short-term usage hazard ratios. However, the fact that hormone therapy hazard ratios for some outcomes differed between the clinical trials and the observational study in Tables 4 and 5 suggests that standard methods for controlling confounding and other biases may be insufficient in a purely observational analysis (e.g., stroke, hip fracture, death from other causes, global index, total mortality). In comparison, the clinical trials "anchored" the analyses presented here and allowed a residual hazard ratio bias factor to be incorporated for the observational study. Such allowance, however, may not have fully addressed the residual confounding issue.

In summary, the results presented here suggest that the unfavorable balance of benefits and risks observed in the CEE/MPA trial as a whole also applies to recently menopausal women. For CEE, benefits and risks appeared to be approximately balanced among recently menopausal women, as was also observed overall in the CEE trial. WHI data provide little support for the estrogen timing hypothesis concerning CHD risk or concerning the benefit-versus-risk summary measures considered here.

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